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THE ANATOMICAL BASIS OF SYNAPTIC TRANSMISSION OF EXCITATION AND INHIBITION IN MOTONEURONS

In memoriam C. S. SHERRINGTON

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Since the existence of specific inhibitory neurons in two parts of the spinal gray matter appears to be an established fact (ECCLES, FATT, LANDGREN, WINSBURY [8]; ECCLES, FATT, KOKETSU [7]) and is highly probable also in the central gray matter of the midbrain for inhibition of oculomotor neurons (SZENTÁGOTHAI and SCHÁB [37]) it seems hopeful to attempt a histological identification of synapses, which exert inhibition on motoneurons. This attempt, however, will be successful only if first different kinds of excitatory synapses, their distribution, size, grouping etc. will be clarified.

At present, two different ways of histological approach of such questions are at our disposal. One is the "*boutons*" or better "*synapses degeneration method*", which has shown itself an important means by which certain pathways can be followed to their very ending on the next link of the neuronal chain. Unfortunately, all hitherto known specific inhibitory neurons are rather short, at most some mm in length, therefore a lesion, by which they can be destroyed or their axons interrupted, must be placed into the closest neighbourhood of the motoneurons. This would be objectionable in the spinal cord, because of the probability of interrupting excitatory fibres running through the region of the lesion, leading thus to uncontrollable results. Fortunately in the midbrain the specific inhibitory cells are at a more favourable site, the lesion of which has no effect on other systems leading to or through oculomotor nuclei. — Another method has recently been developed in this department — originally for histological analysis of the cerebral cortex — which may be called the "*method of remaining elements*". By appropriate interference, small parts of the central nervous system are completely isolated, leaving intact as far as possible the vascular supply of this isolated fragment. In about 4—6 weeks all nervous elements, the cell of origin of which is not surviving in the isolated fragment, undergo degeneration and are resorbed. All of the nervous tissue that remains intact within the isolated part must belong therefore to surviving nerve cells. This method offers some means to investigate short neurons or neuronal connections. Specific inhibitory neurons being short, under certain circumstances the method can be used to analyse their connections.

The main difficulty we are to meet in the investigations presented in the following pages arises from the fact that with spinal cord motoneurons which have been most thoroughly investigated with the aid of intracellular recording techniques, the anatomical situation is rather unfavourable for histological analysis, whereas in oculomotor neurons, where the anatomical situation in many respects is far more favourable, no data furnished by intracellular recording are available.

Material and methods

Cats and dogs were used in these investigations, the former animal mostly for short experiments, the latter in experiments with the "method of remaining elements", postoperative care for several months after serious spinal injury being much easier in dogs. — The operative procedures aiming destruction and subsequent secondary degeneration of presynaptic fibres of motoneurons were the following. Transection of dorsal roots L_5 or L_6 carried out extradurally (in cats and dogs), minute lesions placed with the aid of the HORSLEY—CLARKE technique into different parts of vestibular nuclei, the posterior longitudinal fasciculus, interstitial nucleus of CAJAL, DARKSCHEWITSCH's nucleus and other parts of the anterior midbrain central gray matter (in cats). — Animals were kept alive for 4 or 5 days postoperatively. They were killed under ether anaesthesia, by perfusing rapidly with physiological saline and afterwards with 10% neutralized formol solution. For staining of degenerated terminal fibres and synaptic end-feet in frozen sections, two groups of methods were used: BIELSCHOWSKY methods in the modifications of GROS—SCHULTZE and REUMONT—LHERMITTE, and the NAUTA method. The BIELSCHOWSKY methods, especially the above mentioned modifications, as well as the GLEES method, stain both normal and degenerated terminal fibres and end-feet. Normal end-feet are best stained with the REUMONT—LHERMITTE modification; the CAJAL formulae No. 4, which are the most appropriate to stain most end-feet present, cannot be used here since degenerated terminal structures are stained very incompletely. The situation is unfortunately the same with BODIAN's method. With the BIELSCHOWSKY type methods the exact mode of termination can be investigated and also the relative number and position of normal and degenerated synaptic terminal knobs. To their disadvantage, it is difficult to detect among the many normal elements the degenerated ones, therefore it is hardly possible to trace the preterminal course of the presynaptic fibres, and when only a few degenerated presynaptic fibres are present, these methods may lead to serious errors. The NAUTA methods, on the other hand, allow to suppress staining of the normal elements, with the result that degenerated fragments are easily

detected on the pale background. Unfortunately, the pale staining of normal fibres as well as cells makes it difficult to judge how the degenerated elements terminate. We therefore, as a rule adopted the use of both types of methods in alternating sections of the same material.

For investigation of "remaining elements", two operative procedures were developed. In the first, the "*isolated spinal segment preparation*", the caudal conus of the spinal cord was isolated by temporary crushing with a rigid watchmaker's forceps in two levels about 5 mm apart. The dorsal root filaments entering between the two crushed levels were carefully transected.

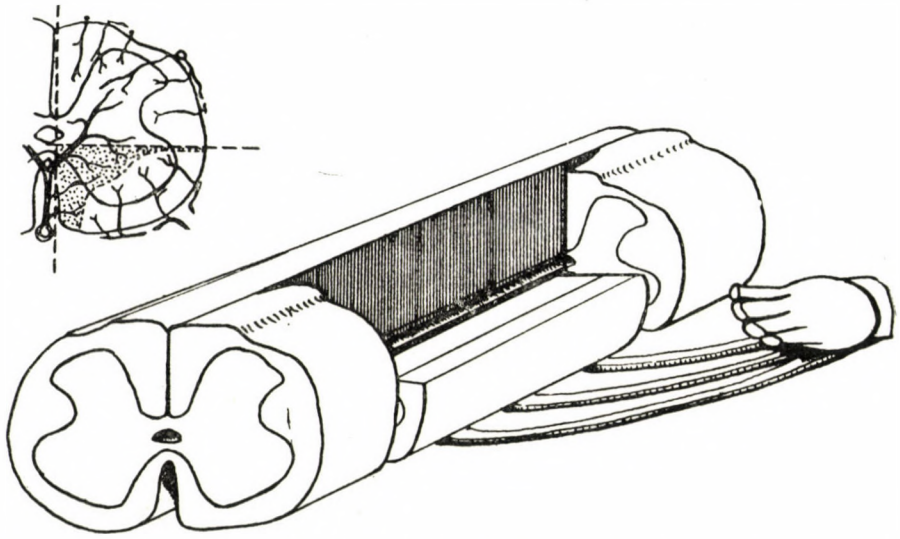

Fig. 1. Preparation of an "*isolated ventral column*". The smaller diagram (left above) shows how the vascular supply of the spinal cord is influenced by the sagittal and horizontal incision (broken lines). The dotted area of the ventral quadrant shows the necrosed zone

By this procedure a small part of the caudal cord is completely isolated from all nervous connections, with the exception of the ventral roots, the vessels of which furnish the blood supply of the isolated part with some vessels which had not been destroyed by the crushing or were soon recanalized after it. The blood supply proved sufficient for the maintenance of most of the neurons in the isolated segment. This preparation serves only as a control for the main experiment with the second preparation, the "*isolated ventral column preparation*". The spinal cord is exposed in the level of L_{6-7} and is split by an incision about 12—14 mm in length in the midsagittal plane. With a rigid watchmaker's forceps one half is crushed twice in the level of the upper and lower end of the longitudinal incision. The dorsal part of the isolated half cord segment is then removed together with the entering dorsal root filaments in a plane perpendicular to the midsagittal, passing through

the central canal (Fig. 1). Aseptic conditions must be maintained very carefully and antibiotics administered for some days after the operation. The blood supply, furnished by the ventral radicular vessels, and others not destroyed in the crushed zones, was sufficient to keep in 5 out of 6 cases the majority of motoneurons preserved. Only the medial part and the central zone of the anterior horn underwent necrosis due to defective circulation, as explained in the upper left diagram of Fig. 1, but, as it will be seen later, this is a great advantage. With appropriate postoperative care the animals were alive in good health, most of them soon relearned to walk on one hind leg. After two months they were sacrificed and the operated part of the spinal cord treated in two different ways. From the part between the crushed zones a transverse disc 2 mm high was excised, fixed in neutral formol and frozen section stained according to the GROS—SCHULTZE and the REUMONT—LHERMITTE methods. The other parts were fixed in BOUIN's solution and after embedding in paraffin serially cut in the longitudinal plane. The serial sections were treated according to BODIAN's protargol method, in order to ascertain that no nervous connections of the isolated part with the cord remained intact. In this respect all cases were successful, since no intact fibre was found crossing the zone between the isolated part and the cord.

Excitatory synapses of spinal motor neurons

Excitatory and inhibitory synaptic terminals can be distinguished histologically if their presynaptic afferent fibres are made separately to degenerate by interrupting the respective pathways. It is advantageous that the Ia afferents of the dorsal root, originating from the annulospiral ending of neuromuscular spindles, are the only ones to establish monosynaptic connections with the motoneurons. Still more important is the fact that this single synaptic connection is excitatory on motoneurons of the muscle from which the Ia afferent arises as well as on the motoneurons of its synergists, and has been supposed to be inhibitory on motoneurons of its antagonists (LLOYD [17, 19]). Since Ia afferents originating from the quadriceps muscle in the cat enter the spinal cord through the roots L_5 and L_6, in which segments are situated also the motoneurons of this muscle, and the motoneurons of its chief antagonist, Biceps-Semitendinosus, are situated more caudally in the level L_7—S_1, transection of the dorsal roots L_5—L_6 will produce secondary degeneration of the excitatory synapses around the motoneurons of the same segments.

We had first performed this experiment many years ago, when nothing was known of the implications mentioned [28]. It is therefore important to focus our attention on some details as number, size, distribution on the cell

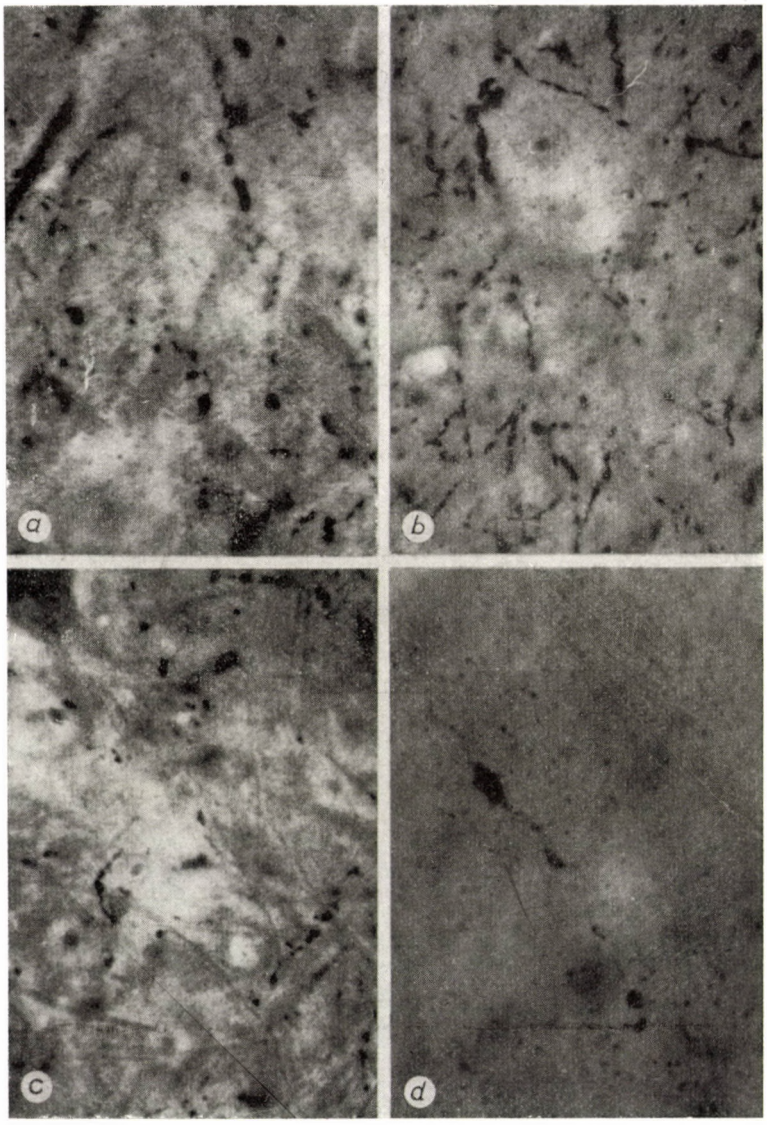

Fig. 2. Degeneration of preterminal fibres in motor nuclei. *a)* Motor horn in L_5 after transection of the dorsal root in the same segment. *b)* 3rd nerve nucleus after transection of the posterior longitudinal fasciculus in pontine level. *c)* 3rd nerve nucleus after lesion of the interstitial nucleus of Cajal. *d)* Degeneration of very thin fibre in the 3rd nerve nucleus after lesion in the region of Darkschewitsch's nucleus. The branches of this fibre are invisible under the light microscope. High power micrograph. Nauta's method, *a–c* magnification ×750, *d* ×3000

surface, grouping, preterminal branching etc. of the degenerated synaptic terminals after transection of dorsal roots, the significance of which had at that time not been known. After radicotomy in L_5 or L_6 the number of degenerated terminal knobs on motoneurons of the same segments is small in comparison with the large number of many hundred end-feet covering each neuron. In NAUTA preparations, at first sight (Fig. 2*a*) degeneration appears to be abundant, but this is due to the degenerated fragments of presynaptic terminal fibres, which are taking part in the intercellular meshwork of the ventral horn nuclei. Since normal fibres are poorly stained in these preparations, the degenerated fragments dominate the picture. In BIELSCHOWSKY type preparations, where due to complete staining of the normal structures the details can be studied more favourably, and degeneration of the presynaptic fibres can be distinguished from that of true terminal knobs, generally only one or two degenerating knobs are detected per motor cell. Considering that one motor cell and the proximal parts of its dendrites will appear in about 5 slides of 15—20 μ thickness, and when allowance is made for half of the end-feet in the state of secondary degeneration left unstained or otherwise undetected, the number of terminal knobs belonging to the monosynaptic pathway of a whole dorsal root will amount in the segment of its entrance to not more than 10—20 per motoneuron. — The boutons terminaux, which degenerate after radicotomy, belong to the largest found on motoneurons. This already appears in NAUTA preparations of the large fragments, indicating that it is the coarser preterminal fibres which are degenerated, those which are known to terminate generally in larger endbulbs. These large synaptic terminal knobs are generally reaching the proximal parts of the main dendrites, then they are running for a while parallel with the dendrites, occasionally forming one or two synaptic enlargements, so called "en-passant" contacts, finally to terminate somewhere near the origin of this dendrite on the somas surface. Branching of these terminals is not frequent. This characteristic course of the larger synaptic terminal fibres is beautifully demonstrated in CAJAL's [4] famous drawing (Fig. 22). It is also worth mentioning that degenerated terminal knobs, which belong to different presynaptic fibres, are never situated close on the surface of the same cell, but rather wide apart.

As regards the numerous other terminal knobs situated on the surface of the motoneurons, it is not possible to determine directly whether they are excitatory or inhibitory in nature. We therefore shall not pay further attention to them.

Excitatory synapses of oculomotor neurons

The situation is far more favourable with oculomotor neurons than with those in the spinal cord. Here we have an extremely powerful pathway,

with only excitatory synapses on motoneurons. It is well known that there is a bi-synaptic pathway between vestibular receptors and extraocular muscles. On stimulating vestibular receptors, especially the cristae, excitatory responses are elicited of some muscles and inhibitory responses of others. If the posterior longitudinal fasciculus is transected in a level above the abducens nucleus excitatory (bi-synaptic) responses are abolished, inhibitory ones preserved ; on the contrary, if in the same level a transection is made leaving intact the posterior longitudinal fasciculus, but destroying its neighbourhood, the excitatory responses are preserved and the inhibitory ones abolished (SZENT-ÁGOTHAI [32, 34]). From this it follows that impulses finally resulting in excitation of oculomotor neurons travel from the vestibular nuclei upward within the posterior longitudinal fasciculus, while impulses that finally cause inhibition of oculomotor cells are ascending somewhere outside this fasciculus. If therefore the posterior longitudinal fasciculus is transected at a pontine level, any degenerated synapse in the 3rd or 4th nerve nuclei may safely be considered as being excitatory.

It is known that the synapses of oculomotor neurons are exceedingly large in lower vertebrates [12] ; when compared with the terminal knobs of other, expecially spinal motoneurons, they are relatively large also in mammals. The preterminal fibres of these large terminal knobs are coarse and generally reach the motoneuron surface near the origin of the main dendrites. Here they divide once or twice and terminate after some large "en-passant" contacts, with large boutons terminaux about 4—5 μ in diameter. Often not only the terminal or "en-passant" knobs, but also some longer part of the preterminal afferent establishes a close parallel contact with the motoneuron surface. — Of course, not all boutons terminaux are so large, about half of the knobs being of regular size, measuring 1—2 μ in diameter.

After transection of the posterior longitudinal fasciculus at the pontine level, practically all of these large end-feet and their preterminal fibres undergo secondary degeneration. This can be seen also from the very large fragments found in NAUTA preparations (Fig. 2*b*). This is even more apparent when this kind of degeneration is compared with that resulting from the lesions of the interstitial nucleus of CAJAL, or transection of the posterior longitudinal fasciculus orally from the 3rd nucleus. Numerous fibres, very probably also excitatory in nature, descend from this nucleus to the oculomotor neurons, where they terminate with small or medium sized terminal knobs, as it appears also in NAUTA preparations (Fig. 2*c*) from the smaller size of the fragments. The interstitial nucleus of CAJAL is, according to our earlier investigations, one of the premotor relay nuclei, conveying cortical and other impulses to oculomotor neurons [30, 31].

Inhibitory synapses of spinal motoneurons

The favourable situation with Ia muscular afferents of dorsal roots in L_{5-6} producing excitation in their own segment and inhibition of motoneurons in the second lower segment would provide an excellent means to study inhibitory synapses, if a direct inhibitory monosynaptic pathway would really exist, as it has been generally supposed. Earlier histological investigations, however, did not support this view, since after transection of the dorsal root L_7 no degeneration of synapses around motoneurons of L_5 was noticed [28]. Later, when the implications of this question became known, we reinvestigated the problem more carefully after transection of the dorsal roots L_5 and L_6. With BIELSCHOWSKY modifications we could not find any degenerated synapses around the motoneurons situated two segments lower (unpublished observations). SPRAGUE [29], working with the NAUTA method, which, as mentioned above, is better suited for tracing degenerated terminal fibres if their number is small, suggests that Ia afferents in lower lumbar segments are giving axo-dendritic terminals to motoneurons situated in the second segment below their entrance. Recently, we have studied the same question again with NAUTA's method and found after transection of the dorsal root L_5 very few axo-somatic knobs degenerated in L_7 motoneurons in a region in which, according to ROMANES [26], Soleus motoneurons are situated, exactly at a site, where ECCLES, ECCLES and LUNDBERG [9] found termination of excitatory collaterals of Ia afferents entering the cord in L_5. Thus far, anatomical evidence does not support the existence of a monosynaptic inhibitory pathway.

Inhibition of motoneurons is brought about, according to the investigations of ECCLES, FATT, LANDGREN and WINSBURY [8] and ECCLES, FATT KOKETSU [7] made with the intracellular recording technique, by the activity of two types of specific inhibitory neurons, one of which is situated in the intermedio-medial nucleus of CAJAL, the others being the so-called "Renshaw cells" of the anterior horn. It is suggested that Ia afferents are terminating with excitatory synapses on the inhibitory cells of the intermedio-medial nucleus, the activity of wich exerts inhibition on motoneurons. This assumption is strongly supported by anatomical evidence. From GOLGI preparations it has been known since long that collaterals of dorsal root fibres terminate in the intermedio-medial nucleus [3;15], and they have been traced also with the aid of the boutons-degeneration method [28]. — Another type of inhibition is supposed to be produced by the so-called "*Rensh w-cells*" situated in the region where the ventral root fibres are collected to leave the ventral horn. According to ECCLES and al. [7], the initial collaterals of motoneuron axons, also well-known from GOLGI preparations, excite by means of a cholinergic mechanism the *Renshaw-cells*. Short axons of these cells are supposed to

terminate on motoneuron somas or the initial parts of the dendrites with inhibitory synapses. This inhibitory pathway offers an excellent opportunity for histological control and also for the identification of at least one kind of inhibitory synapses.

Abundant degeneration of collaterals leading to the intermedio-medial nucleus is found in the entrance segment after transection of the dorsal roots L_5 or L_6. They constitute a separate bundle running in medioventral direction (Fig. 3), from the basis of the dorsal horn towards the intermedio-medial

Fig. 3. Degenerated bundle of collaterals running toward the intermedio-medial nucleus of Cajal. Segment L_5 after transection of the dorsal root in the same segment

region. After arriving there they turn upwards or downwards and ascend or descend in the intermedio-medial region, where they terminate in the neighbouring and the second cranial or caudal segments. Some but not too many fibres of the dorsal root, which finally terminate in the intermedio-medial nucleus of the neighbouring segments, are entering the gray column only in the next or second caudal segment from their entrance into the cord. There are many degenerated fragments around some intermedio-medial neurons, while in the neighbourhood of others no degeneration is noticed. This is due very probably to two facts ; (i) the terminal knobs of this region are rather

large [11], and consequently their preterminal fibres are relatively coarse, (ii) one presynaptic fibre gives more terminal branches to the same cell or, alternatively, there is a convergence of dorsal root collaterals originating from the same segment upon certain intermedio-mediate neurons, while other neurons of the same region receive collaterals only from another segment. It is not possible to judge from histological preparations, which of the two possibilities holds true. In some preparations we could trace a few degenerated collaterals in the second segment below the transected root, running from the intermedio-medial nucleus along the medial border of the ventral horn to the region where the ventral root fibres leave the gray matter, *i.e.* the region where the *Renshaw-cells* are supposed to be. Their number being small, it was not possible to determine the exact site of their ending. — So far histological evidence very much supports the view of ECCLES et al. on the pathway of "direct inhibition" in the lower lumbar cord. Unfortunately, direct investigation into the connections of these specific inhibitory cells with motoneurons is not possible with our present histological means, since any lesion, however small and exactly placed into the region of inhibitory cells, would cause the degeneration of an uncontrollable number of other fibres also terminating on motoneurons.

We, therefore, must base our further attempts on the other type of inhibitory cells. In "*isolated segment preparations*" of about 5 mm length the motoneurons are fairly well preserved with a large part of their pericellular network, and a small number of medium-sized or small terminal knobs, with their preterminal fibres and usual neurofibrillar structure completely left intact. Especially numerous terminal knobs are found around smaller cells in the ventral part of the anterior horn. Since all nervous elements, found intact in these isolated preparations, must take their origin from the neurons of the isolated part itself, these findings indicate that motoneurons as well as other smaller neurons within the ventral horn receive terminal knobs from cells situated in the same segment. However, these intact nerve-endings cannot be attributed, or at least not all of them, to inhibitory synapses, since most of the dorsal root afferents, as well as the longer pathways, do not terminate directly on motor, but rather on internuncial neurons. These internuncials must have numerous excitatory synapses on motoneurons also of the same segment. By physiological (LLOYD [18]), as well as anatomical means [33], the main maximum length of these internuncials (descending) has been determined to be about three segments, but naturally nothing can be said on the shortest distance, which is bridged by excitatory internuncials. There is, however, no reason to deny the existence of excitatory connections being not longer than the distance between the dorsal horn or the intermediate region and the motoneurons of the same level. The findings in these isolated segment preparations therefore only serve as controls, which indicate that

the isolation of a small part of the spinal cord does not necessarily lead to degeneration or atrophy of the terminal knobs of motor radicular cells.

With the "*isolated ventral horn preparation*" the situation is completely different. Internuncial neurons are present in the ventral horn, but their majority is situated in the medial and the central part of the ventral column. On these cells descending longer pathways, — especially the tecto-spinal, interstitio-spinal and, very probably, also the reticulo-spinal tracts, — terminate. The medial internuncials of the ventral horn are giving synapses mostly to motoneurons of the contralateral side, only the central ones for those of the ipsilateral side [33]. Very fortunately, in our isolated ventral horn preparations, because of the insufficient blood supply due to the sagittal incision, by which the chief vessels of the gray matter entering from the depth of the anterior median fissure are destroyed, only the lateroventral half of the anterior horn remains intact (Fig. 1 left, top), this being supplied by the anterior radicular and pial vessels. Therefore, in these preparations almost exclusively true motoneurons and some smaller cells remain intact, which are situated between the ventral root fibres gathering before leaving the gray matter. Any terminal fibre or synaptic terminal found intact in this preparation must either belong to motoneurons or to the so called "*Renshaw-cells*", so that any synaptic structure on motoneurons must — if the conception of ECCLES, FATT and KOKETSU [7] is correct — be considered as an inhibitory one.

However carefully we studied several hundred otherwise fairly intact motoneurons in "*isolated motor horn preparations*", only occasionally was an intact terminal knob found. In the rather sparse intercellular network nevertheless many extremely fine fibres were found intact, which on the basis of their staining properties and general histological character were considered as terminal ramifications of axons. Their diameter was generally extremely small, some tenths of a micron or even less, so that often they were hardly visible with the highest resolving power of the light microscope. During their course they occasionally formed strange coils, so that they resembled intact terminal fibres found in CLARKE's column after complete deafferentation of the lower cord (SZENTÁGOTHAI and ALBERT [36]).

The relation of these fine intact fibres to the motoneuron somata and proximal parts of the dendrites is often very intimate. Sometimes a real meshwork of such extremely fine fibres even appears closely to envelop the surface of the motoneuron (Fig. 4). — These fibres generally pass unseen in normal silver stained preparations, because the picture is dominated by the coarser preterminal branches of the terminal knobs, and also as very probably they are mostly not stained in normal material, the available silver being consumed during the reduction process by the larger nervous structures with stronger argentaffinity, as often experienced in similar cases.

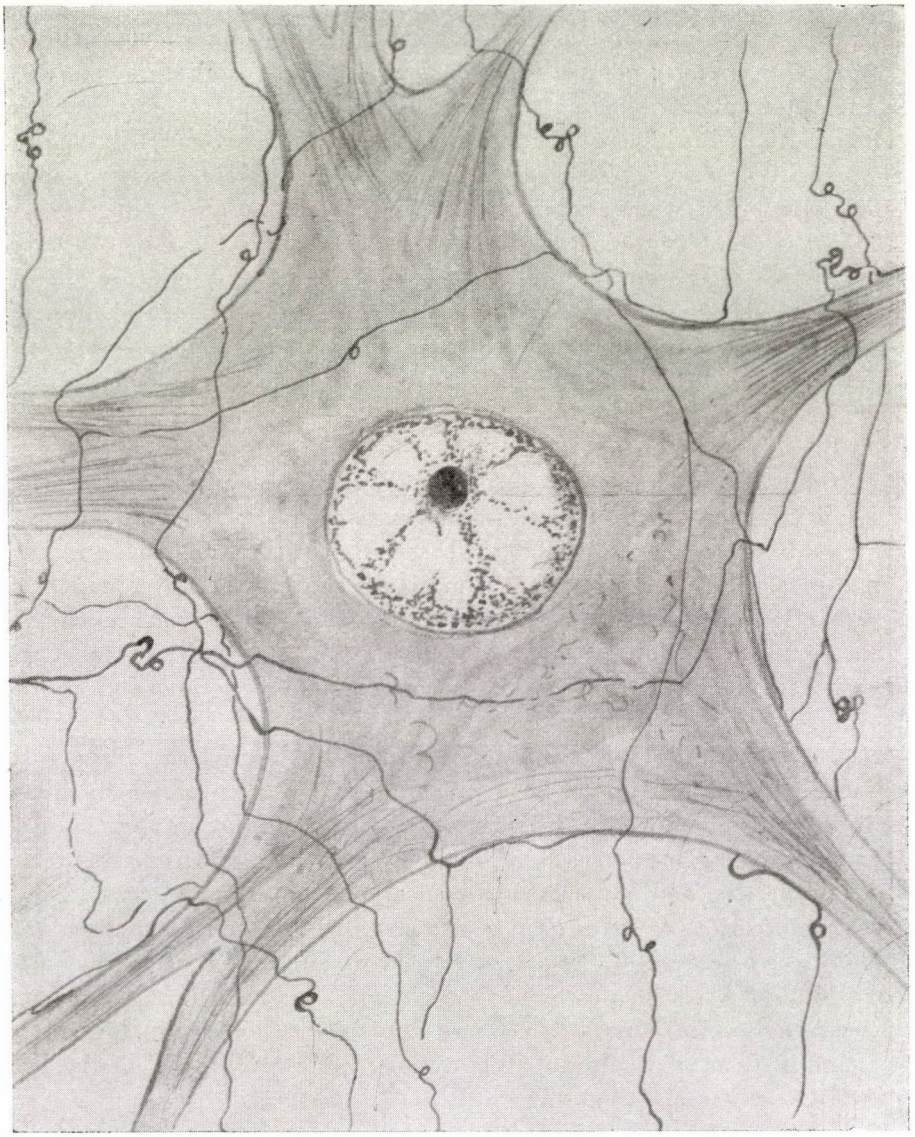

Fig. 4. Motoneuron of an isolated ventral column preparation, 2 months after isolation. Intact very fine terminal fibres with characteristic "coils", no terminal knobs

On the smaller cells situated ventromedial from the motoneuron groups, generally between the gathering bundles of the ventral root fibres, *i.e.* exactly where the *Renshaw-cells* are located by the physiologists, completely intact terminal knobs were found with their usual neurofibrillar structure and smoothly contoured preterminal afferent fibres (Fig. 5). On one cell several

intact terminal knobs were found, very probably belonging to different preterminal fibres. — This not only indicates that the lack of boutons terminaux around motoneurons is not due to some failure of the staining technique, the possibility of which in case of a negative result with silver preparation has always to be considered with the utmost care, but also that terminal

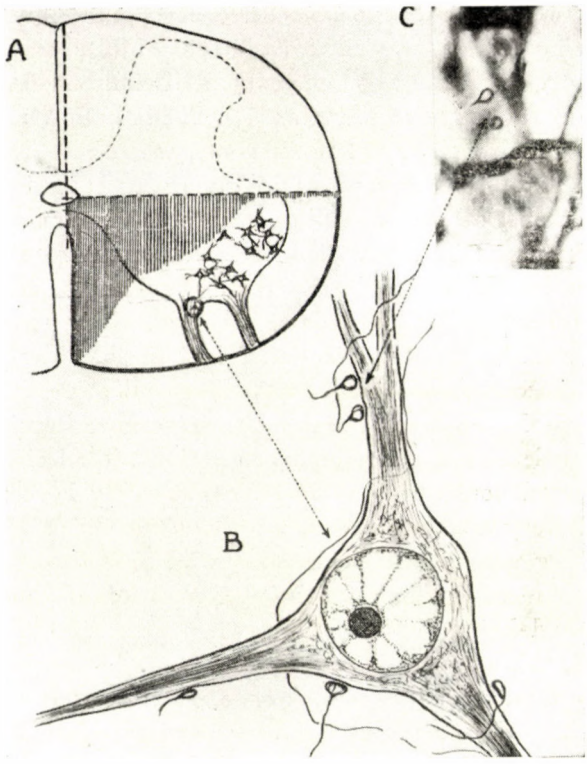

Fig. 5. Intact terminal knobs of Renshaw cell. A. The circle shows situation of the nerve cell presented in B.; C. shows high power micrograph of two terminal knobs

knobs can survive in such preparations undamaged, if only their cells of origin are preserved.

From these findings the preliminary conclusion can be drawn that (i) the anatomical situation seems to be in complete accordance with the pathways of the so called "antidromic inhibition" as postulated by ECCLES, FATT and KOKETSU [7] up to the point of the *Renshaw-cells*; and (ii) that inhibitory influence — at least what concerns antidromic inhibition — is not exerted upon motoneurons by ordinary boutons terminaux of any kind or localization.

Inhibitory synapses of oculomotor neurons

As already mentioned in the introduction, the anatomical circumstances for investigation of inhibitory synapses are much more favourable in the oculomotor nucleus. Vestibular impulses, that finally result in inhibition of oculomotor neurons, travel somewhere outside the posterior longitudinal fasciculus proper and are directly conveyed to neurons of the anterior central gray matter of the midbrain, especially those of DARKSCHEWITSCH's nucleus. Electric stimulation of this region completely inhibits even the strongest reflexes of extraocular muscles to currents artificially evoked in the semicircular ducts (SZENTÁGOTHAI and SCHÁB [37]). The situation here is completely analogous to the spinal pathway of Ia afferents, with the only difference that secondary ascending vestibular neurons are giving direct excitatory collaterals to oculomotor neurons, others ascending outside the fasciculus excite specific inhibitory short neurons in the region of DARKSCHEWITSCH' nucleus. After lesions within the lateral vestibular nucleus, abundant sings of degenerated synapses are found around many cells of this region, the character of which in all respects resembles the degeneration found in the interomedial nucleus of CAJAL after transection of dorsal roots. Since no other fibres originating in, or transversing, the nucleus of DARKSCHEWITSCH are running to or through the oculomotor nucleus, any sings of degeneration after lesion of the former region, found around oculomotor neurons, could safely be considered as the remnants of inhibitory synapses. — In a previous study [32] we had already sought signs of degeneration in such cases with the aid of BIELSCHOWSKY techniques, but could find none ; *i.e.* no degeneration of boutons terminaux. The NAUTA method being more suitable when the number of degenerated elements is small, this question was reinvestigated. A very careful selection of our experimental material was necessary to ascertain that neither the posterior commissure, nor the pretectal region or the interstitial nucleus of CAJAL and the posterior longitudinal fasciculus were severed, since these nuclei and tracts are known to contribute presynaptic excitatory fibres to the oculomotor nuclei. All cases in which the lesion had however slight affected these regions, were discarded. Those considered above (5 cases), were all cases of isolated lesions of the anterior central gray matter of the midbrain, immediately anterior and rostrad from the oculomotor nucleus. The border of the lesion in one case was as near as 200 μ to the anterio-dorsal border of the 3rd nucleus (EDINGER—WESTPHAL division).

Sings of degeneration of very fine fibres were in those cases detected in the oculomotor nucleus, in NAUTA preparations and later, knowing what to look for, also in preparations treated according to the BIELSCHOWSKY modifications. The fibres undergoing degeneration are mostly near to the limits of the resolving power of the best oil immersion systems. Their degener-

ated fragments are small and not easily found, only occasionally can the beaded fragments be recognized well (Fig. 2*d*), but the finer branches of these degenerated fibres soon escape observation. A comparison with the signs of degeneration in the same nucleus after lesions of the vestibular nuclei (Fig. 2*b*), photographed with one fourth of the magnification used in Fig. 2*d*, gives an impression of the differences in size between these fibres and the excitatory terminal knobs and their preterminal branches. Most of the degenerated fine fibres are descending through the oculomotor nucleus in dorso-ventral direction, to form finally a sparse network in the region where the initial segments of the oculomotor axons begin to gather before leaving the gray matter. The number of these fine degenerated fibres is, however, too small to allow a clear impression of the mode of their termination. Unfortunately, they escape observation under the light microscope in the course of their branching. Their relation to some motoneurons seems to be fairly close, and even more so with the initial part of their axons, but no terminal formation was detected which could have been considered as some synaptic connection with the initial segment of the motoneuron axon, *e.g.* spirals, etc.

Discussion

The results presented suggest that pathways conveying excitatory impulses terminate on motoneurons with common terminal knobs. No special localization of the knobs belonging to a certain presynaptic pathway has been noticed in motoneurons. The excitatory collaterals of lower lumbar Ia afferents give only few preterminal branches to the same motoneuron, and excessive branching of a collateral for different motoneurons in the same level seems also improbable. They terminate on motoneurons with the largest type of terminal knobs on the soma surface, after one or two "en-passant" contacts, generally established with the proximal parts of the main dendrites. Before terminating, they only occasionally branch once or twice for the same motoneuron. Terminal knobs, belonging to different collaterals of Ia afferents of the same segment, are never localized on the same motoneuron close to one another, but are scattered wide apart over the cell surface. This finding, demonstrated by us many years ago [28], indicates that a strategic grouping of terminal knobs, in contrast to the assumption of Lorente de Nó [22], cannot be of significance for spatial summation in the case of transmission of excitation from Ia afferents to motoneurons. — This again is in fair accordance with the results of intracellular recording, especially with the constant time course of the excitatory postsynaptic potential and the theory of origin of the impulse in the initial segment of the motoneuron axon (Eccles [6]). The small number of terminal knobs per motoneuron belonging to the Ia afferents of a whole segment is difficult to explain. Making allowance for all

difficulties in estimating the number of degenerated synaptic end-feet, this number cannot be more than 10—20 per motoneuron. This would barely suffice to secure spatial summation, — in absence of major internuncial bombardment, — considering that, according to intercellular recording, about ten impulse must converge in a motoneuron in order to produce a postsynaptic potential high enough to generate an impulse (BROCK et al. [1]). The mean minimum size of postsynaptic potentials being 1 mV, *i.e.* the postsynaptic potential generated by one presynaptic fibre, and the threshold for impulse generation of motoneurons about 10 mV, it is difficult to imagine how a maximal volley from a muscle nerve can secure effective spatial summation, even if it is assumed that the major part of the Ia synaptic knobs on any motoneuron originates from the same muscle nerve. But this would be again inconsistent with the fact that the same motoneuron can be activated by the Ia afferents of different muscles. Some other explanation might be necessary before the exact mode of transmission of excitatory impulses and especially of spatial summation will satisfactorily be understood (*c.f.* LLOYD and MCINTYRE [21]; HUNT [13] on transmitter potentiality).

The difference between the mode of synaptic articulation of the same Ia afferents with motor and CLARKE nucleus neurons is quite remarkable (SZENTÁGOTHAI and ALBERT [36]). In the latter, very long parallel and series of "en-passant" contacts between the presynaptic fibre and the postsynaptic soma-dendritic surface are dominant. The presynaptic fibres are often coarse and are branching excessively for the same CLARKE neuron. They often terminate with extremely large boutons terminaux on the cell somas. Similarly very large terminal knobs, but no parallel contacts, have recently been found in this laboratory by ROZSOS [27] among the synapses of primary afferents with the neurons of BURDACH's nucleus. For both types of synapses the high probability of impulse transmission, *i.e.* a relative lack of spatial summation, are characteristic (LLOYD and MCINTYRE [20]; THERMAN [38]). It might, therefore, be interesting to study the significance of the size of the articulation surface areae for synaptic transmission of impulses.

One is generally inclined to consider synapses with large contact surface between two neurons as those with high probability of transmission and the reverse. This is especially apparent in some synapses without any convergence. Beautiful examples of such synapses are found in invertebrates (BULLOCK [2]; YOUNG [41]) in which spatial summation being impossible, the transmission of any presynaptic impulse is certain. The same kinds of synapses also occur in vertebrates. The basket-like or cup-like synapses in the dorsal cochlear or the trapezoid nuclei, and the similar synapses in the ciliary ganglia of reptiles and birds first described by Lenhossék [16], are mostly synapses of 1 : 1 relation between pre- and postsynaptic neurons. The contact surface in all these is large and involves a considerable fraction (30—50%) of the postsynaptic cell surface. Strangely, all these are lacking dendrites, or have very short irregular ones, which often develop only late in life. — According to the modern concepts of synaptic transmission (ECCLES [6]), an excessive enlargement of the synaptic contact surface would render the transmission mechanism ineffective due to large cleft resistance relative to membrane resistance. The synaptic cleft, according to electron microscope pictures, seems to have a universal width of about 200 Å. — From some histological descriptions of these large synapses the conclusion might be drawn that however large the synaptic

contact surface in these cases, it is not a closed surface, but, due to the excessive branching of the presynaptic terminal, divides into thin elongated contact stripes. More close cytological analysis has, however, shown,— at least in the case of the ciliary ganglion synapses of birds, — that the synaptic articulation surface is in reality much larger and also more closed than appears from silver preparations [35], the main portion of the presynaptic terminal being built up by non-argentaffine plasma. In the ciliary ganglion synapses of birds we even detected fine, non-argentaffine branches of the presynaptic terminal, which protude into deep channels of the postsynaptic cell body. — It is perhaps important to mention that all these synapses with excessively large articulation surface are known as excitatory. — In order better to understand the significance of the size and arrangement of terminal knobs on motoneurons it will be necessary to study the mode of synaptic transmission in these large-surface synapses with the aid of modern microphysiological methods.

Concerning the synapses of inhibitory function, our knowledge is even less satisfactory. When direct inhibition had become known, and even more before that time, it was generally supposed that the same presynaptic fibres are giving off excitatory collaterals to the motoneurons of one muscle, and inhibitory ones to the motoneuron pool of its antagonist. This, however, is made rather improbable by two theoretical points. If synaptic transmission occurs by the action of some specific transmitter substance, the principle of Dale [5] must be applied, according to which the same chemical transmitter is released from all synaptic terminals of the same neuron. Support has been given to this principle by recent advances in the biology of nerve cells, especially on the mode of constant reproduction of neuroplasma in and in the neighbourhood of the nucleus [14], and its constant distal flow in the axons [39], as well as the important rôle played by mitochondria in nerve terminals. These circumstances all indicate that the neuron as a self-reproducing unit is very unlikely to have a certain metabolic activity at one of its terminal branches and a completely different one at another. — Difference in location of the synaptic terminal on the surface of the postsynaptic cell might produce a contrary effect without any difference in metabolic setup or chemical activity of synaptic terminals. Recent physiological evidence, at least what concerns motoneurons, does not give much support to this view [6]. With the exception of the interesting spiral axon-hillock synapse in Mauthner neurons (RETZLAFF [25]), no histological evidence is known in favour of this assumption. — The opposite view of the possible rôle of synapses with the more distal parts of the motoneuron dendrites, proposed on a histological basis independently by SPRAGUE [29] and ourselves [37], cannot be reconciled neither with more recent histological findings, nor with the time course of the inhibitory postsynaptic potential, which indicates that inhibition must be exerted on motoneurons somewhere on the soma, or the most proximal parts of the dendrites.

Another still more important, though purely theoretical argument against the assumption of excitatory and inhibitory collaterals given by the same (premotor) neuron, emerges from an analysis of the integration of movements. It is a very convenient abstraction to consider muscles or muscle groups as arranged in simple antagonistic pairs, but almost never true in the living organism. Let us consider *e.g.* the action of extraocular muscles in an animal with a frontal position of the eyes, cat or monkey or man. Elevation of the visual axis is brought about by the contraction of the pair *Superior rectus — Inferior obliquus* and reciprocal relaxation of the pair *Inferior rectus — Superior obliquus*. Downward movement is accomplished by a reverse action. Rotation of the eye around the visual axis, as it is very common in vestibular reflexes, is produced by the joint action of the pairs *Superior rectus — Superior obliquus* vs. *Inferior rectus — Inferior obliquus*. Especially beautiful examples of such different combined actions can be evoked by labyrinthine receptors, where the stimulation of the same receptor *e. g.* by displacement of the utricular otolithic membrane in different directions throws the above four extraocular muscles into action in the same combinations as mentioned above (SZENTÁGOTHAI [34]). — The same holds true for all muscles acting on a joint or joints with more than one axis, *e.g. Extensor carpi radialis, — ulnaris and Flexor carpi radialis, — carpi ulnaris* in man, which, working in different combinations, produce wholly different movements. — If the same premotor neurons would terminate with excitatory synapses on the motoneurons of one muscle and inhibitory ones on those of its antagonist, these two muscles would, according to our present knowledge concerning synaptic transmission, be linked together reciprocally once and all. It would be impossible to bring them to simultaneous contraction, since the inhibitory collaterals would crosswise inhibit the motoneuron pools of both muscles, unless the very improbable situation is assumed that different sets of premotor, etc. neurons exist for all possible combinations of muscle action. An appreciation of this side of the problem of inhibition had been given in the description of the reflectory connections of different isolated labyrinthine receptors with extraocular muscles (SZENTÁGOTHAI [34] pp. 70—71), before anything had become known of the existence of specific inhibitory neurons. — A very simple solution of the problem is given by the incorporation of one specific inhibitory neuron into the

inhibitory limb of the pathway, as shown in the diagram of Fig. 6. Let us suppose that any one of the premotor neurons PM_{1-4} (naturally representing a pool of similar neurons) has, beside excitatory connections with the respective motoneurons M_{1-4}, synapses with two of the specific inhibitory cells i_{1-4} and $i_{1'-4'}$, connected with the motoneurons of two muscles out of its three potential antagonists. If the inhibitory cells are synaptically connected not only with their respective motoneurons, but also, as seen in the diagram, with one another, in case of simultaneous discharge of *e.g.* the two premotor neurons PM_1 and PM_2, the motoneurons M_3 and M_4 would be effectively inhibited by the specific inhibitory neurons $i_{1'}$ and $i_{2'}$, whereas,

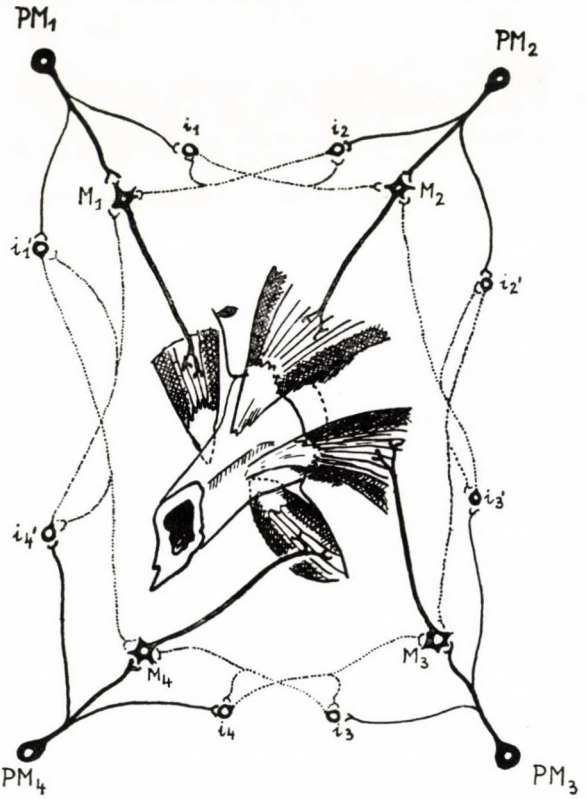

Fig. 6. Diagram for explanation of the action of specific inhibitory cells in case of reciprocal innervation of 4 muscles acting in different combinations on a sphaeroid joint

due to crosswise inhibition of the neurons i_1 and i_2 by each other, excitation of the motoneurons M_1 and M_2 could occur without hindrance. The same would hold true for any other combination of simultaneous discharge of two premotor neurons of the diagram, with the result that always two motoneurons would be excited and the remaining ones inhibited. This diagram is naturally a speculative one, but it explains in a very simple way the necessity of the existence of specific inhibitory neurons for the integration of muscular function in all cases when not only fixed antagonistic pairs have to be brought into action. The diagram postulates that the specific inhibitory neurons are in mutual interconnection. This, at least in the *Darkschewitsch* nucleus region, is really the case, where in Golgi preparations the numerous interconnections of the neurons, even between those of the two sides by collaterals, can be seen fairly well.

These rather theoretical considerations are in complete accordance with the conclusion of ECCLES et al. [8] on the non-existence of direct inhibitory collaterals of Ia spinal afferents to motoneurons, as well as with the negative

result of all attempts to trace after transaction of the dorsal roots degenerated collaterals to motoneuron groups which are inhibited by the Ia afferents entering through that root.

There is, up to a certain point, also a complete agreement between physiological and anatomical information concerning the pathways of inhibition. The pathway of direct inhibition, as well as the predictions of ECCLES, FATT and KOKETSU [7] on the pathway of antidromic inhibition, have been verified most satisfactorily by anatomical evidence. From the results with the "*isolated ventral horn preparations*" it clearly appears that the collaterals of motoneurons really terminate on smaller cells situated exactly where the "*Renshaw cells*" are supposed to be localized. This synapse is of the boutons-terminaux type, which, according to all evidence furnished by these investigations, must be considered as of exclusively excitatory character.

Unfortunately, the problem of the inhibitory pathway from the specific inhibitory cell to the motoneurons remains unsettled. We can draw but the negative conclusion that *inhibition is not exerted on motoneurons by terminal knobs of any kind or localization*, nevertheless, on the basis of these incomplete and by no means satisfactory positive histological findings, we venture to offer some possible explanations, being at the same time well aware of their fallibilities.

(i) It might be possible that the sparse meshwork of fine fibres remaining intact in isolated ventral horn preparations, is in fact the terminal ramification of the *Renshaw cells*. (An alternative explanation would be that it is nothing else than motoneuron axon collaterals.) The *Renshaw cells* might perhaps be considered some kind of *Golgi* cells, the terminal axon ramifications of which, — due to their extremely small diameter, — evade observation under the light microscope. FERNÁNDEZ—MORÁN [10] has described even in spinal tracts submicroscopic unmyelinated fibres visible only with the aid of the electron microscope, so that the discovery of terminal fibres and synaptic structures, much finer than those hitherto known, would not be unexpected. The thin degenerated fibres, the ramifications of which escape further observation, found in the oculomotor nucleus after lesions of DARKSCHEWITSCH's nucleus, could be explained in the same way. — The very fine, so called "coiled fibres" detected after complete deafferentation of the lower cord in CLARKE's column [36], are very similar to the "remaining fibre meshwork" in isolated ventral column preparations. Their exact termination on *Clarke* neurons could not be determined. Since inhibition of *Clarke* neurons has been described by LAPORTE, LUNDBERG and OSCARSSON [23], it might be possible that these fine fibres arising from neurons localized somewhere in the neighbouring gray matter, may be the histological substrata of this effect.

The paucity of these structures, however, if considered as the anatomical basis of inhibition, does not seem to be easily reconciled with the abundance

of the excitatory structures represented by the great mass of terminal knobs. The physiological events which accompany excitation and inhibition, on the other hand, are rather symmetric, one being more or less the mirror image of the other. — Another difficulty arises from the small diameter of the inhibitory terminal fibres. It is questionable whether the low conduction velocities we must suppose in so extremely fine fibres, even considering the short distances, can be reconciled with the time course of events.

(ii) With respect especially to the findings on oculomotor nuclei, another possibility cannot be simply rejected. Here the sings of degeneration, following lesions placed into regions where the specific inhibitory neurons are localized, are relatively abundant in the ventral part of the 3rd nucleus, where the initial not myelinated parts of the motoneuron axons begin to gather into bundles. Though no signs of some specific synaptic structure between the degenerated fibres and the motoneuron axons have ever been seen, it might nevertheless be possible that the meshwork of these fine fibres exerts its inhibitory influence upon the initial segment of the axon. — Working with the histology of synapses it must constantly be kept in mind, how difficult even the largest forms of synaptic terminals are to stain. Therefore the fact that nobody has hitherto found any kind of synapse on the initial segment of the axon of motoneurons, does not necessarily prove that there really exist none. — Of course, recent observations with the aid of intracellular recording are not in favour of such an assumption.

(iii) Finally, we cannot completely reject the idea that we are perhaps on the wrong track, when we by all means try to explain the action of the specific inhibitory cells upon motoneurons exclusively on the basis of some kind of synaptic mechanism. The meagre histological findings of degeneration following destruction of a cell group the excitation of which produces such a spectacular effect of complete inhibition of oculomotor neurons [37] might indicate that we have to search after mechanisms fundamentally other than in case of excitatory impulse transmission.

Summary

An attempt has been made histologically to identify the synapses that transmit excitation and inhibition of motoneurons. — The investigations have been based partly on the method of secondary degeneration of synapses, but in order to study the very short connections occurring in the inhibitory pathways a new method of neural isolation of smaller parts of the spinal cord has been developed. After a longer period of degeneration the remaining elements of the isolated parts of the gray matter have been studied.

All fibre systems which convey excitation to motoneurons, terminate with the well-known terminal knobs. Size, number, distribution, localization and preterminal branching of synapses belonging to different excitatory systems have been described.

Inhibitory pathways, known hitherto only from physiological evidence, could be traced by anatomical methods to the different groups of specific inhibitory neurons. The synapses by which these specific inhibitory neurons are activated, being thus excitatory ones, belong also to the boutons-terminaux type.

The connections of the specific inhibitory cells with motoneurons could not be satisfactorily identified, but the results nevertheless clearly indicate that inhibition is not exerted upon motoneurons by any type of the hitherto known terminal knobs. A sparse network of extremely fine, almost submicroscopic, fibres may be derived from the inhibitory neurons, which is in fairly close contact with the motoneurons. The possible significance of this meshwork as an inhibitory synaptic formation has been discussed.

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АНАТОМИЧЕСКИЕ ОСНОВЫ ПЕРЕДАЧИ ВОЗБУЖДЕНИЯ И ТОРМОЖЕНИЯ НА ДВИГАТЕЛЬНЫЕ НЕЙРОНЫ

Я. СЕНТАГОТАИ

Автор пытается гистологически отождествлять раздражающих и тормозящих синапсов двигательных нейронов. Исследования основываются отчасти на методе вторичного перерождения синапсов, однако, для исследования короткой интерневральной связи, предположенной на тормозящем пути, автор применяет новый метод. Небольшая часть переднего рога спинного мозга совершенно изолируется от невральных связей, а затем, после несколько месячного периода дегенерации исследуются неповрежденные невральные элементы изолированной части.

Все системы путей, которые передают импульсы возбуждения к двигательным невронам, заканчиваются на поверхности этих клеток с общеизвестными двигательными пластинками. Подробно излагаются величина, число, организация и место двигательных пластинок, относящихся к различным премоторным системам, также как и условия разветвления приводящих волокон.

Предположенные до сих пор исключительно на основании физиологических опытов, проведенных с помощью внутриклеточного отведения, тормозные пути можно анатомически проследить вплоть до специфических тормозящих невронов. Синапсы, раздражающие специфические тормозящие клетки (значит тоже возбуждающие), также типа двигательных пластинок.

Автору не удалось гистологически удовлетворительным образом отожествлять связь между специфическими тормозящими клетками и двигательными невронами, однако, на основании его наблюдений является несомненным, что непосредственные тормозящие синапсы двигательных невронов не принадлежат к типу двигательных пластинок. С определенной вероятностью можно предполагать, что из тормозящих клеток происходит весьма тонкая, почти субмикроскопическая сеть нервных волокон, которая находится в тесной касательной связи с поверхностью двигательных невронов. Автор взвешивает ту возможность, что морфологический субстрат непосредственной передачи торможения на двигательные невроны следует искать в этой сети.

ANATOMISCHE GRUNDLAGEN DER SYNAPTISCHEN ÜBERTRAGUNG VON ERREGUNG UND HEMMUNG BEI MOTONEURONEN

J. SZENTÁGOTHAI

Es wurde der Versuch unternommen, die Erregung und Hemmung auf motorische Neuronen übertragenden Synapsen mittels histologischer Verfahren zu identifizieren. Die Untersuchungen beruhen einesteils auf der Anwendung des Verfahrens der sekundären Degeneration von Synapsen. Zwecks Studium kürzerer Neuronenverbindungen, wie sie gerade bei den Leitungsbahnen der Hemmung physiologischerseits angenommen werden, wurde eine neue Methode der neuralen Isolation kleinerer Teile des Rückenmarkes eingeführt; nach einer längeren Zeitspanne der Degeneration wurden im isolierten Gebiete der grauen Substanz die zurückbleibenden Nervenelemente studiert.

Alle Fasersysteme, die motorischen Neuronen Erregung zuführen, endigen an ihrer Oberfläche mittels der allgemein bekannten Held-Auerbachschen Endfüsschen. Grösse, Zahl,

Anordnung und Lokalisation der zu verschiedenen prämotorischen Systemen gehörenden Endfüsschen und die Verzweigungsart ihrer zuführenden Fasern wird beschrieben.

Leitungsbahnen der Hemmung, die bisher nur auf Grund physiologischer Beobachtung angenommen wurden, konnten anatomisch bis zu den Gruppen spezifischer Hemmungsneuronen exakt verfolgt werden. Die Synapsen mittels derer diese Hemmungsneuronen erregt werden, also ebenfalls Erregungssynapsen, sind sämtlich auch vom Endfüsschentyp.

Die Verbindung der spezifischen Hemmungsneuronen mit motorischen Neuronen konnte histologisch nicht zufriedenstellend identifiziert werden. Es konnte lediglich sichergestellt werden, dass diese Synapsen keinesfalls zu dem Endfüsschentyp gehören. Ein lockeres, aber aus äusserst feinen, fast submikroskopischen Fasern bestehendes Geflecht konnte mit etlicher Wahrscheinlichkeit aus den spezifischen Hemmungszellen hergeleitet werden, dessen Beziehungen zu den motorischen Neuronen ziemlich eng sind. Eine mögliche Rolle dieses Geflechts als unmittelbarer Überträger der Hemmung auf Motoneuronen wird besprochen.

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